

NAMHC Concept Clearance – September 20, 2004

Presenter: Kathy L. Kopnisky, Ph.D.
Chief, Neuropathogenesis Program
Center for Mental Health Research on AIDS (CMRHA)
Division of Mental Disorders, Behavioral Research and AIDS (DMDBA)

Proposal for “HIV and Psychiatric Comorbidity Basic Research Project”

The NIMH plans to solicit research proposals addressing the biological and genetic factors underlying the high comorbidity between HIV-1 infection and psychiatric disorders. Epidemiological studies indicate that the majority of HIV-1 infected individuals will suffer from a psychiatric illness, ranging from a depressive episode to clinical depression, anxiety, or psychosis during the course of their infection. The presence of such disorders often promote additional complications in that these individuals are less likely to adhere to medication regimes and are more likely to overuse or abuse alcohol and illicit drugs, all of which are high-risk activities with serious consequences on disease progression and HIV-1 transmission.

Viral infections, particularly neurotropic infections, can cause persistent and progressive changes in emotional and cognitive functions as well as alterations in gene expression and synaptic activity. Viral-induced imbalances in neuronal network functioning may subsequently precipitate or accentuate psychiatric conditions in the context of a vulnerable brain or genetic predisposition. Furthermore, research indicates that psychiatric illnesses and HIV-infection of the central nervous system may target similar brain structures, neurocircuitry and receptor systems. Findings of *gene x environment* (G X E) interactions in genetic psychiatry include the identification of specific polymorphisms in neurotransmitter system genes and resultant proteins (e.g. 5-HTT), which were associated with vulnerability to mental illness in the context of stressful life events. Similarly, ethanol and opioids, substances of abuse frequently found in populations with mental illness, have been shown to facilitate HIV infection of central nervous system cells and to be associated with an increased risk of perinatal transmission of HIV, prompting research questions regarding the physiological basis of the drug-induced transmission or facilitation of HIV. Furthermore, researchers have shown that endogenous stress responsive hormones can modulate chemokine receptors (the HIV-1 coreceptor for viral entry) and can enhance HIV-1 replication in human blood cells; reciprocally, HIV-1 can enhance the expression of stress responsive hormones, thereby eliciting a feed-forward cycle.

We propose studies broadly directed at determining: (1) the genetic and biological underpinnings of comorbid HIV-1 infection and psychiatric illnesses; (2) the mechanisms by which psychiatric illness or HIV-1 infection influences the comorbid disease course and contributes to inter-individual variability in disease progression; (3) the vulnerable brain structures, neurocircuitry systems, or other substrates involved in comorbid disease progression; (4) the effect of HIV on the developing brain (model of HIV⁺ children or MTC transmission) and mature brain as pertains to elucidating vulnerable G X E or other interactions and immune profiles (or mediators) most likely to influence psychiatric conditions; and (5) developing pharmacological agents that not only negatively impact on the ability of HIV to infect cells or replicate, but also could alleviate the symptoms of depression, anxiety or other psychiatric disorders.

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